(2)

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	31 March 1979	Final/ 1 Apr 1979-31 March 1979

4. TITLE AND SUBTITLE
THE EFFECT OF HIGH Gz FORCES ON SYMPATHETIC NERVOUS ACTIVITY

5. FUNDING NUMBERS

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8. PERFORMING ORGANIZATION REPORT NUMBER
1664

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
AFOSR
BLDG 410
BAFB DC 20332-6448

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
AFOSR-78-3601

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Plasma epinephrine, norepinephrine and dopamine-beta-hydroxylase were used to quantitate the degree of sympathetic activation undergone by miniature swine and by men. Swine exposed to high Gz forces have massive output of norepinephrine which falls off rapidly during return to 1 G. Repeated exposures are characterized by a further increase of norepinephrine demonstrating large reserve stores and increased norepinephrine to prolonged stress. These animals also had a massive adrenomedullary output of epinephrine during the stress of high Gz and epinephrine output was even greater after repeated stresses. High Gz exposed swine increased circulating levels of dopamine-beta-hydroxylase and greatly increased levels after five exposures to high Gz. Dopamine-beta-hydroxylase levels, unlike those of norepinephrine and epinephrine, may provide a measure of sympathetic nervous stress that occurred minutes or hours in the past. Human subjects exposed to high Gz forces had basal norepinephrine levels and norepinephrine levels after the termination of high Gz similar to miniature swine. People who have severe head injuries have increased circulating norepinephrine and are subject to development of myocardial lesions.

14. SUBJECT TERMS	15. NUMBER OF PAGES
	24
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
unclassfied	unclassified		

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1664

AFOSR-TR-80-[redacted]

FINAL TECHNICAL REPORT AFOSR GRANT #78-3601

THE EFFECT OF HIGH Gz FORCES ON SYMPATHETIC NERVOUS ACTIVITY

ABSTRACT:

We studied the effect of high + Gz forces on sympathetic nervous activity and the potential for circumstances which elevate sympathetic nervous activity to cause cardiac damage. Plasma levels of epinephrine, norepinephrine and dopamine-beta-hydroxylase were used to quantitate the degree of sympathetic nervous activation undergone by adult miniature swine and by men. Swine exposed to high + Gz forces have a massive output of norepinephrine during exposure which falls off rapidly during return to 1 G. Repeated exposures to high + Gz are characterized by a further increase in output of norepinephrine demonstrating large reserve stores of this neurotransmitter and increased output of norepinephrine in response to prolonged stress. These same animals also had a massive adrenomedullary output of epinephrine during the stress of high + Gz and epinephrine output was even greater after repeated stresses. This epinephrine secretion is maladaptive to maintenance of blood pressure and may participate in the development of cardiac lesions in the swine. Dopamine-beta-hydroxylase is secreted along with epinephrine and norepinephrine and has a much longer half-life in the blood. During high + Gz exposure the swine increased their circulating levels of dopamine-beta-hydroxylase and greatly increased their levels after five exposures to high + Gz. Dopamine-beta-hydroxylase levels, unlike those of norepinephrine and epinephrine, may provide a measure of sympathetic nervous stress that occurred minutes or hours in the past. Human subjects exposed to high + Gz forces had basal norepinephrine levels and norepinephrine levels after the termination of high + Gz similar to those found in adult miniature swine. Thus, the animal model appears to be pertinent to sympathetic nervous events occurring in man during high + Gz.

People who have severe head injuries have increased circulating norepinephrine and the more severe the injury the higher the norepinephrine levels become. These people are subject to development of myocardial lesions similar to those seen in adult miniature swine during high + Gz exposure and have a very high incidence of electrocardiographic abnormalities. It is possible for men to develop cardiac lesions similar to those previously noted in the adult miniature swine, and these lesions may be caused by the release of endogenous catecholamines.

THE SYMPATHETIC NERVOUS RESPONSE TO HIGH + GZ FORCES IN THE ADULT MINIATURE SWINE:

In work performed with Dr. Russell Burton and associates at the Biodynamics Branch of the USAF School of Aerospace Medicine, Brooks Air Force Base, Texas, we evaluated the sympathetic nervous response to high + Gz forces in adult miniature swine. This animal is susceptible to cardiac pathology associated with high sustained + Gz (Burton and MacKenzie, 1976). Studies in other mammals have demonstrated that infusion of exogenous catecholamines can lead to cardiac pathology and so it was of interest to determine the levels of endogenous catecholamines secreted by the adult miniature swine in response to this stress. Under exceleration with high + Gz forces, there is a decrease in blood pressure to the carotid arteries where the major baroreceptors are located. This initiates a reflex discharge of sympathetic nerves which help restore blood pressure by secreting norepinephrine which constricts blood vessels and stimulates the heart. At the same time, if the animal has an emotional response to this severe stress, it will have an adrenal discharge of epinephrine and norepinephrine. The secretion of epinephrine is even more potent in stimulating the heart but is not nearly so effective in maintaining blood pressure as is sympathetic neuronal secretion of norepinephrine. We measured these substances in blood from three adult miniature swine exposed to a simulated air combat maneuver lasting 100 seconds with exceleration up to + 9 Gz. Prior to the experiment, the swine had plasma norepinephrine levels of 0.4 ± 0.08 ng/ml and had plasma epinephrine levels of 0.1 ± 0.03 ng/ml. This same experiment was repeated five times and the stress of preparation for the experiment lead to a considerable increase in circulating catecholamine levels before the animals were ever exposed to the stress of high + Gz. (See Table 1).

Blood was sampled from the swine before, during, immediately after and two minutes after an exposure to 100 seconds of high + Gz forces. The norepinephrine response to this stress is shown in Figure 1.

As can be seen in Figure 1, the animals had a massive response of circulating plasma norepinephrine to the stress of high + Gz. These levels of plasma norepinephrine are higher than we have ever documented in people and should elicit a maximal response of sympathetic nervous elements. The fall-off of plasma levels of norepinephrine is very rapid with an estimated half-life of about one minute. This is somewhat more rapid than prior estimates of catecholamine half-lives of two to three minutes that had previously been made. We suspected that after such a massive sympathetic nervous discharge that the sympathetic nerves might become depleted of reserve norepinephrine and then there would be a diminished response of circulating norepinephrine in response to an identical stress. To evaluate this, animals were exposed to five high + Gz runs on the same day and then plasma samples taken for a repeat measurement of plasma norepinephrine. Contrary to our expectations, norepinephrine levels were consistently higher during the fifth simulated air combat maneuver than during the first. The percent difference in norepinephrine is most strikingly increased before and two minutes after the simulated air combat maneuver demonstrating that these animals were continuing to secrete high levels of norepinephrine even while the specific stress of high + Gz forces was not occurring. This result, while somewhat reassuring in that it demonstrates that mammalian sympathetic nervous systems have an enormous reserve capacity, is also disconcerting in the implication that after prolonged stress animals maintain a continuous and possibly inappropriate output of norepinephrine.

DOPAMINE-BETA-HYDROXYLASE AFTER EXPOSURE TO HIGH + GZ FORCES:

Dopamine-beta-hydroxyase (DBH) is the enzyme which synthesizes norepinephrine from dopamine. The enzyme is present in vesicles in noradrenergic nerve terminals with norepinephrine. When a noradrenergic nerve is stimulated it releases norepinephrine and DBH. Norepinephrine is rapidly inactivated and has a very short plasma half-life of from one to three minutes. Thus a plasma norepinephrine level obtained very long after a stressful event cannot give an evaluation of the measure of sympathetic stress that occurred during that event. DBH, however, has a very long plasma half-life. Thus, a sympathetic nervous stress that causes a large release of norepinephrine and DBH can be detected at a later time through measurement of plasma levels of DBH. On the other hand, DBH levels should not be expected to show as dramatic a rise after a sympathetic nervous stress as norepinephrine since at any time there is a large amount of circulating DBH present because of its long half-life. Figure 3 shows DBH levels in the same swine whose norepinephrine and epinephrine levels are shown in Figures 1 and 2. During the first air combat maneuver DBH levels rise a small amount and then fall slightly two minutes after the end of the ACM. After five simulated air combat maneuvers DBH levels have increased markedly from the contribution of sympathetic nervous discharge that occurred during all five ACM procedures.

The plasma level of DBH appears to provide a measure of sympathetic nervous stress that has occurred over a longer period of time. It may be a worthwhile tool in evaluation of stress undergone by pilots actually flying aircraft since limitations on when blood can be sampled precludes measurement of plasma norepinephrine in these pilots. A measure of plasma DBH in pilots who undergo simulated air combat maneuvers in a centrifuge and then actually fly aircraft could help determine if actual air combat maneuvers provide a significantly greater stress than simulated air combat maneuvers in a centrifuge.

HUMAN STUDIES:

Norepinephrine Levels in Pilots Subjected to High + Gz Forces: As can be seen in Figure 4 when blood is drawn from men who have undergone a force of 7 G there is a marked increase in plasma levels of norepinephrine which appears to be linear with increasing duration of exposure to high + Gz. The basal levels of plasma norepinephrine of these subjects are about normal for sitting subjects (Lake et al., 1976). The average level of G force to which these subjects were subjected is similar to the G force to which swine were subjects for 100 seconds in prior experiments and norepinephrine levels of about 5,000 pg/ml one minute after exposure are similar to those of swine two minutes after G exposure. It thus appears that both basal levels of norepinephrine and norepinephrine levels after high + Gz exposure are quite similar in man and swine and that the adult miniature swine may serve as an appropriate model for sympathetic nervous stress undergone by man in response to high + Gz forces.

The Head Injured Human as a Model of Heart Damage From Excess Sympathetic Nervous Activity: Burton and MacKenzie (1976) have found that when the adult female miniature swine is exposed to G forces in the range of those men are exposed to while flying combat aircraft that these animals can develop sub-endocardial hemorrhage and stress cardiomyopathy (Burton and MacKenzie, 1976; MacKenzie and Burton and Butcher, 1976). Animal studies alone cannot clarify

cardiac abnormality was not suspected.

The anatomically demonstrated cardiac lesions consisted uniformly of superficial areas of subendocardial hemorrhage and necrosis. Adjacent myocardial fibrosis was noted in one case. The lesions were clustered on the left side of the intraventricular septum and occasionally involved the papillary musculature. This type of lesion is very similar to that previously described in the adult miniature swine by Burton and MacKenzie (1969).

In the prospective study monitoring of the ECG was carried out in a consecutive series of brain injured patients with head injury from spontaneous intracerebral hematoma or trauma. The ECGs were abnormal in 89% of the patients. These abnormalities were minor in only five or 13% of the patients. As shown in Table 4, the ECG abnormalities included 31 cases of ST interval prolongation as well as 21 cases of T-wave changes. Other abnormalities included disorders of rhythm, rate and conduction.

All of the six patients who died had abnormal ECG findings (Table 5). Post-mortem examination was performed on four of these patients. Gross and microscopic examination of the heart revealed myocardial fibrosis in one case; the other cases had no acute cardiac lesions.

The patients with positive ECGs tended to have more severe head injury. The overall mean-coma score was 9.3 for all patients. The mean score of those patients with negative ECGs was 13.6, while that of the patients with positive ECGs was 9.

Norepinephrine levels were determined in 61% of the patients. Sixty-three percent of these patients had elevated serum norepinephrine levels (greater than 550 pg/ml). Of the 17 patients with elevated norepinephrine, 16 of them had abnormal ECGs. As can be seen in Figure 5 patients with low coma scores who were most severely head injured had the highest plasma norepinephrine levels.

There clearly appears to be a relationship between ECG changes and brain injury and also a relationship between brain injury and elevations in norepinephrine levels. The fact that 16 of the 17 patients with elevated norepinephrine levels had abnormal ECGs suggest that increased sympathetic nervous activity is causal in the development of ECG abnormalities in head injury. The retrospective study showed pathologic evidence of cardiac changes characterized by focal changes in the bundle of His and left intraventricular septum. There is a high concentration of sympathetic nerve endings to the heart in the area of the septum where cardiac damage was observed. The relationship between elevated serum norepinephrine levels and ECG abnormalities suggest that there may be an excess of catecholamine release in these endings, which may produce the conduction changes and myocardial damage observed.

These studies demonstrate that after head trauma man is susceptible to the type of cardiac lesions demonstrated by Burton and MacKenzie (1969) in swine exposed to high + Gz. A common event occurring in these two circumstances is increased catecholamine secretion.

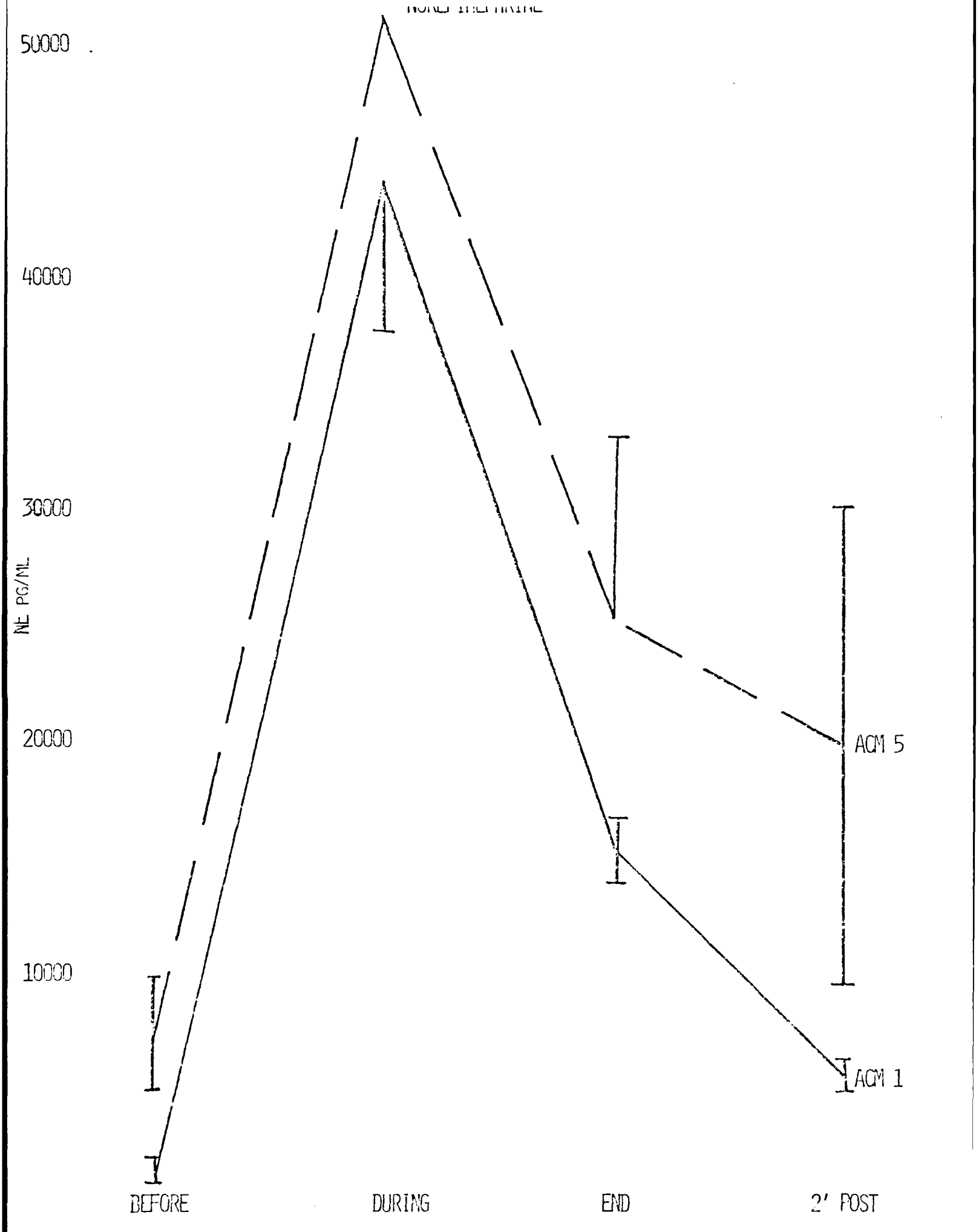

50000
40000
30000
20000
10000
NE PG/ML
ACM 5
ACM 1
BEFORE
DURING
END
2' POST

FIGURE 2: Levels of plasma epinephrine in adult miniature swine exposed to high + Gz forces for 100 seconds. Refer to Figure 1.

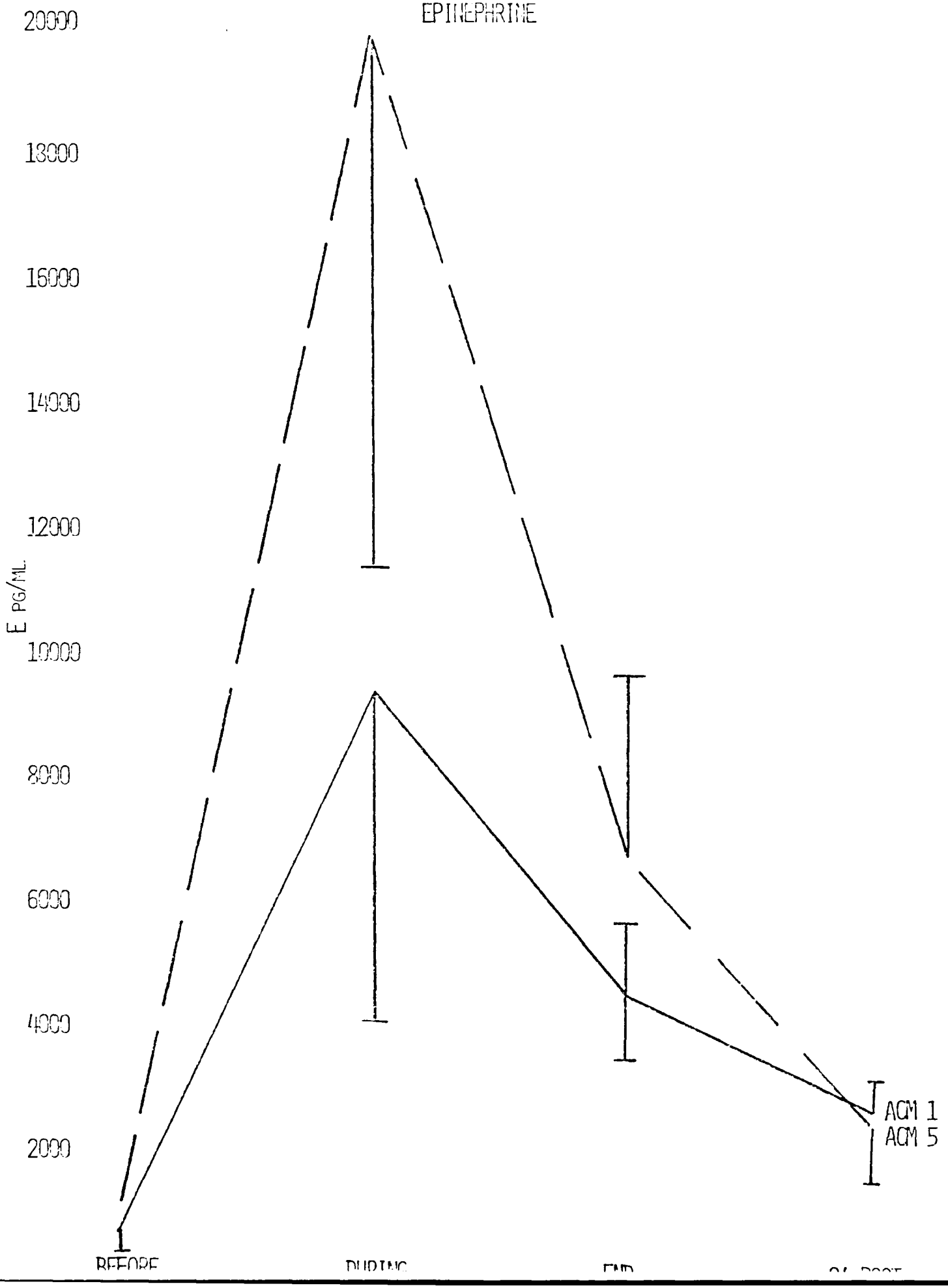

EPINEPHRINE
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
E PG/ML
ACM 1
ACM 5
BEFORE
DURING
END

FIGURE 3: Plasma levels of dopamine-beta-hydroxylase in adult miniature swine in response to exposure to 100 seconds of high + Gz. Refer to Figure 1.

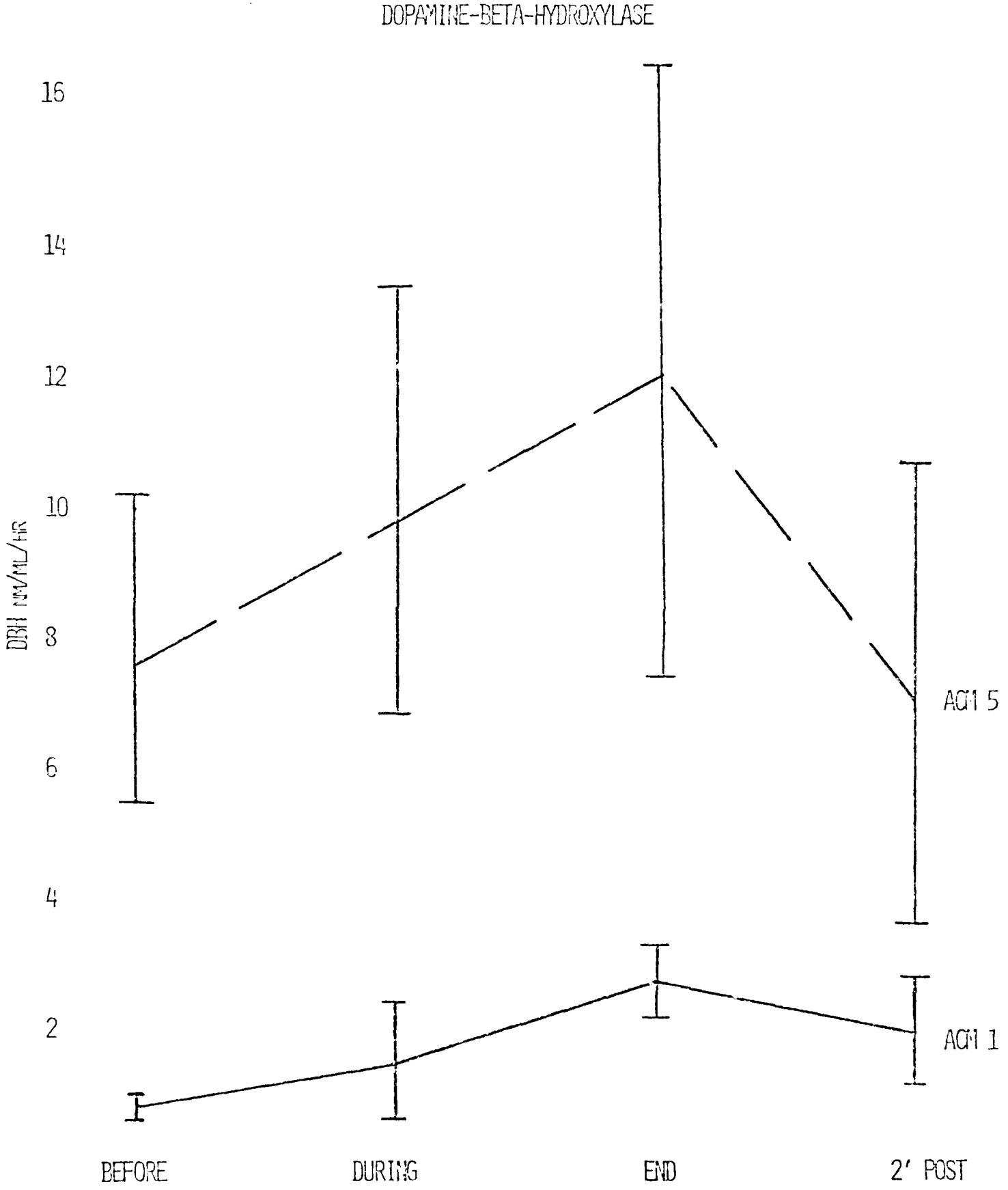
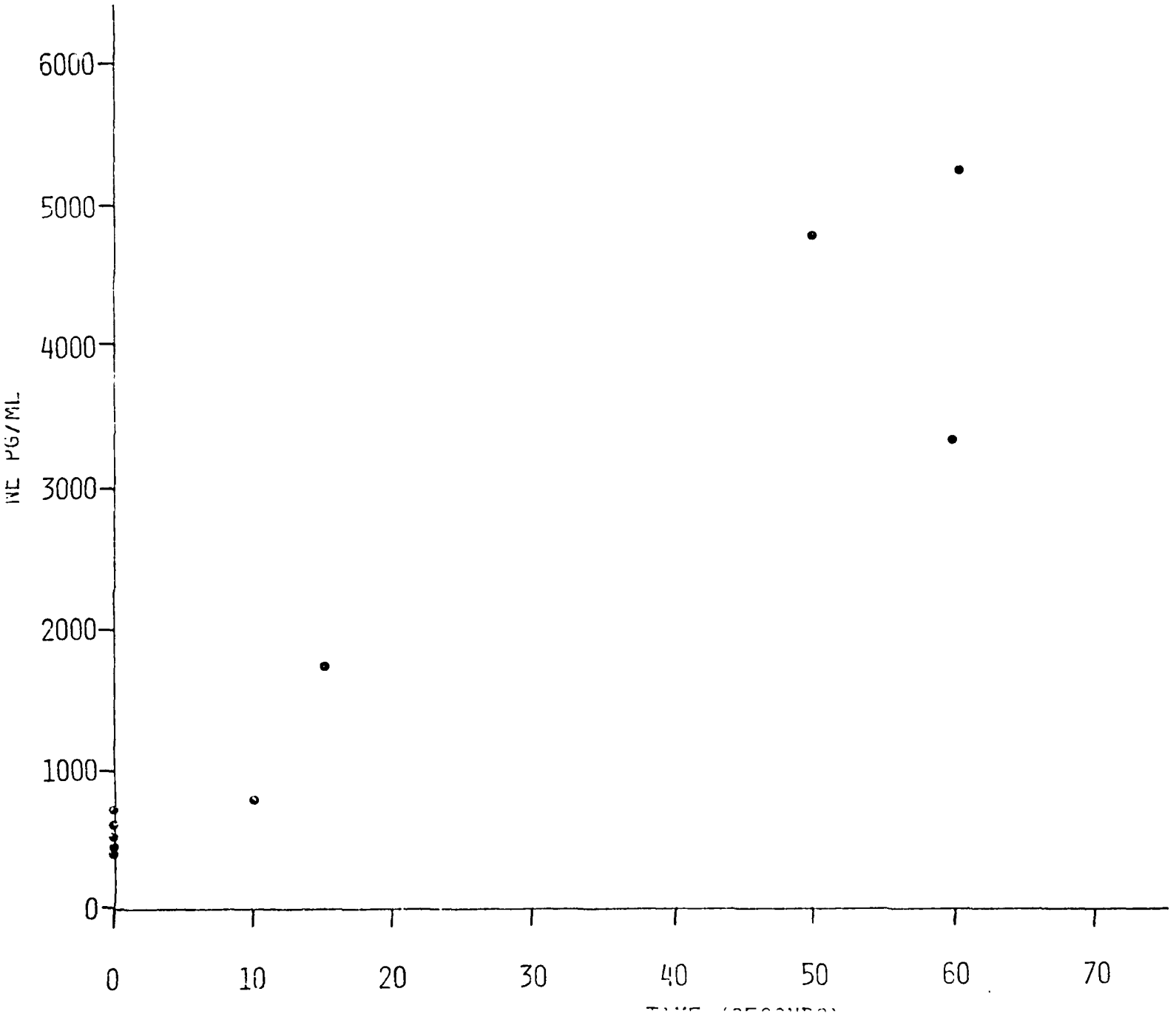

DOPAMINE-BETA-HYDROXYLASE
16
14
12
10
8
6
4
2
DBH NM/ML/HR
ACH 5
ACH 1
BEFORE
DURING
END
2' POST

FIGURE 4: Plasma norepinephrine levels of five subjects who underwent a force of + 7 Gz for from 10 to 60 seconds. Blood samples were drawn an average of one minute after the termination of high + Gz exposure.

NE LEVELS OF 5 SUBJECTS AFTER 7 G FOR 10 - 60 SECONDS



RELATIONSHIP BETWEEN SERUM NOREPINEPHRINE LEVEL AND COMA SCORE

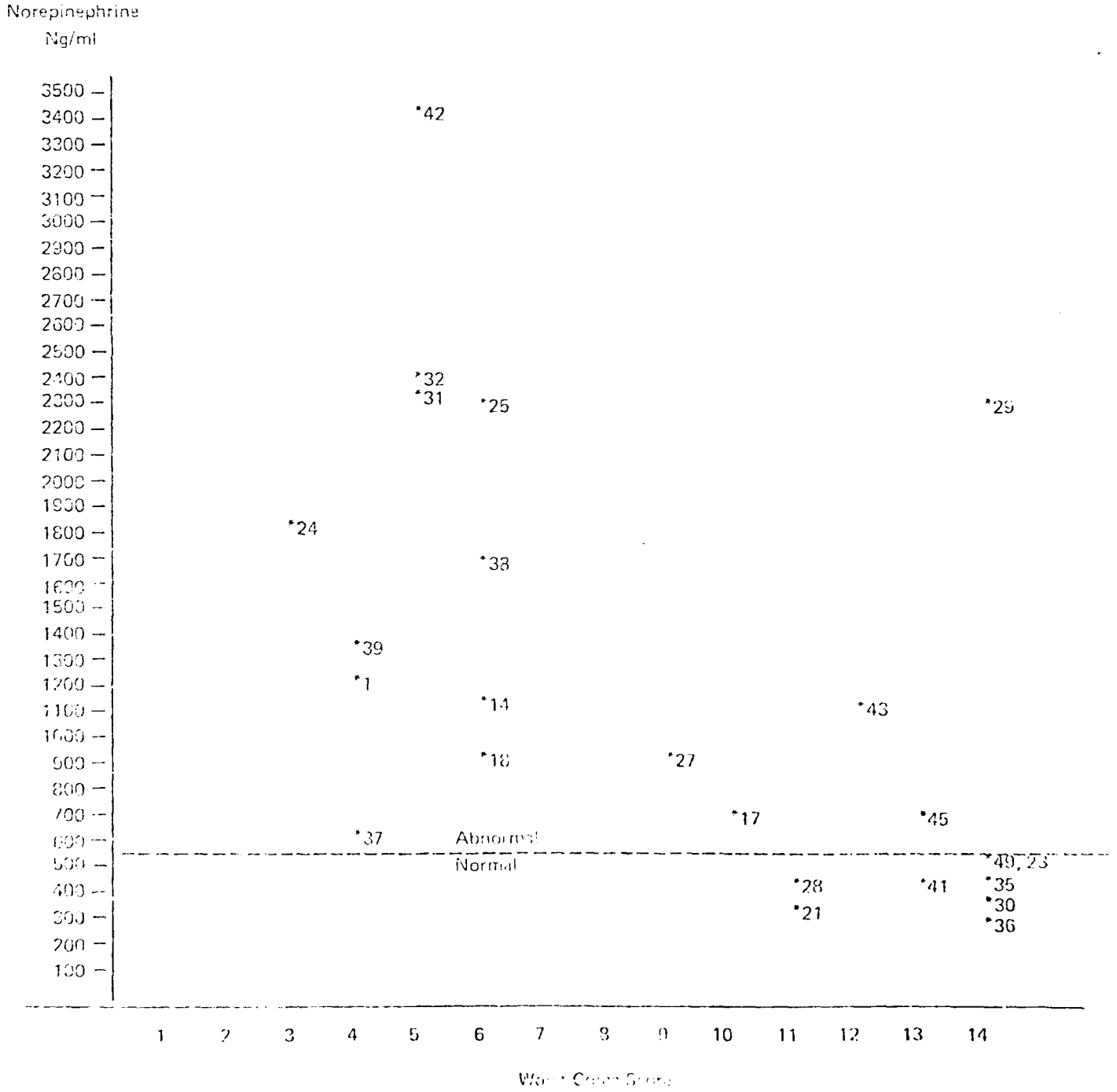


TABLE 1

EFFECTS OF STRESS OF PREPARATION FOR HIGH + GZ EXPERIMENTS ON PLASMA NOREPINEPHRINE AND EPINEPHRINE

State of Animal	Relaxed	Prior to ACM 1	Prior to ACM 5
Plasma Norepinephrine (ng/ml)	0.4 ± .08	1.5 ± .4	7.4 ± 2.7
Plasma Epinephrine (ng/ml)	0.1 ± .03	0.8 ± .3	1.0 ± .0

TABLE II

CLASSIFICATION OF ECG ABNORMALITIES

I. MINOR

1. Prolonged QT Interval (corrected)
2. Tachycardia
3. Bradycardia

II. MAJOR

1. Wandering Pacemaker (Arrhythmia)
2. Premature Ventricular Contractions
3. Hypoxic
   a. ST Changes
   b. Inverted T Waves
   c. Frank Infarction

TABLE III

CARDIAC ABNORMALITIES IN 28 FATAL HEAD INJURIES - RETROSPECTIVE ANALYSIS

CASE #	AGE	SEX	DIAGNOSIS	SURVIVAL DAYS	ECG DONE	ECG ABNORMAL	HEART
1	20	M	Subdural Hematoma	8	No	--	+
2	17	M	Intracerebral Hematoma	1	No	--	-
3	40	M	Subdural Hematoma	8	No	--	-
4	27	M	CHI	2	No	--	+
5	63	F	Subdural Hematoma	2	No	--	-
6	29	M	CHI	11	Yes	Yes	+
7	19	M	CHI	0.5	No	--	-
8	63	M	Depressed Fx	18	No	--	-
9	40	M	Intracerebral Hem.	26	Yes	No	-
10	24	M	Intracerebral Hem.	2	No	--	-
11	21	M	Intracerebral Hem.	6	Yes	Yes	-
12	4 mos	F	Subdural Hematoma	1	No	--	-
13	16	M	Subdural Hematoma	3	No	--	+
14	33	M	Intracerebral Hem.	1	No	--	+
15	16	M	CHI-Basilar Fx	0.5	Yes	Yes	-
16	53	M	CHI	54	Yes	Yes	-
17	51	F	CHI	5	No	--	+
18	20	M	Epidural Hematoma	2	No	--	-
19	45	M	Depressed Fx	0.5	Yes	Yes	-
20	40	M	Subdural Hematoma	20	No	--	-
21	65	M	CHI	8	Yes	Yes	-
22	17 mos	M	CHI	5	No	--	+
23	42	M	CHI	0.5	No	--	-
24	33	M	GSW	8d	No	--	+
25	16	M	CHI	1	Yes	Yes	-
26	41	F	Acute Subdural Hem.	13	Yes	Yes	-
27	70	M	CHI	10	Yes	Yes	-
28	43	M	Intracerebral Hematoma	0.5	No	--	-

TABLE IV

ECG ABNORMALITIES IN 9 FATAL HEAD INJURIES

Retrospective Study

CASE #	AGE	SEX	DIAGNOSIS	SURVIVAL	ECG FINDINGS	ANATOMIC HEART FINDING
6	29	M	Depressed Fx	11 days	Serious Tachycardia Peaked T Waves	Subendocardial Hemorrh
11	21	M	Intracerebral Hematoma	6 days	Serious Tachycardia Peaked T Waves Prolonged QT Interval	Head only examined
15	16	M	CHI	1 day	Prolonged QT Interval	Heart Negative
16	53	M	Intracerebral Hematoma	54 days	Prolonged QT Interval Bradycardia	Heart Negative
19	45	M	CHI	1 day	Atrial Fibrillation	Heart Negative
21	65	M	CHI	8 days	Serious Tachycardia Paroxysmal Atrial Tachycardia ST Segment Elevation Prolonged QT Interval	Heart Negative
25	16	M	Hypoxic Encephalpathy	1 day	Serious Tachycardia Prolonged QT Interval	Heart Negative
26	41	F	Acute Subdural Hematoma	13 days	Serious Tachycardia Paroxysmal Atrial Tachycardia ST Segment Elevation Prolonged QT Interval	Heart Negative
27	70	M	CHI	10 days	Serious Tachcardia LVH Prolonged QT Interval	Heart Negative

TABLE V

ECG ABNORMALITIES IN 38 SURVIVING PATIENTS*

QT Interval Prolongation	-	31 cases
T Wave Inversion	-	21 cases
ST Segment Depression	-	8 cases
Arrhythmias (atrial fibrillation, ectopic beats)	-	5 cases
Tachycardia	-	2 cases
Wandering Pacemaker	-	2 cases
A-V Block	-	1 case
Bradycardia	-	1 case
Premature Ventricular Contraction	-	1 case

*
Most patients had more than 1 abnormality.
5 patients had no ECG abnormalities.

TABLE VI

ECG ABNORMALITIES IN 6 FATAL BRAIN INJURIES

Prospective Study

CASE #	AGE	SEX	DIAGNOSIS	SURVIVAL	ECG FINDINGS	AUTOPSY CARDIAC FINDINGS
9	67	M	Intracerebral	4 days	Minor - Prolonged QT Interval Major - Left Atrial Arrhythmia ST Depression	No Post
13	50	M	Intracerebral Hematoma	5 days	Minor - Prolonged QT Interval Major - Wandering Pacemaker	Heart Negative
19	67	M	Intracerebral Hematoma	9 days	Minor - Prolonged QT Interval Major - Myocardial Infarction Pattern	Myocardial Fibr
24	6	M	Intracerebral Hematoma	62 days	Minor - Prolonged QT Interval (Only 1 ECG performed after neurologic deterioration)	No Post
31	45	M	Multiple Intracerebral Hematomas	10 days	Minor - Prolonged QT Interval Major - Left Atrial Abnormality ST Segment Depression	Heart Negative
37	64	M	Depressed Fx with Intra-cerebral Hematoma	5 days	Minor - Prolonged QT Interval Tachycardia Major - T Wave Inversion	Heart Negative

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